REMARKS

Claims 1-40 were pending in the application. Claims 1, 11 and 13 have been amended herein and claims 41 and 42 have been added. Claims 5-7, 9, 12, and 14-16 have been cancelled, without prejudice, as being drawn to a non-elected invention. Claims 17-40 have been cancelled by previous amendment, and claims 2-4 and 10 have been cancelled herein, without prejudice. Upon entry of this amendment, Claims 1, 8, 11, 13 and 41-42 remain pending.

Support for the amendments to the claims and new claims added may be found in the specification and claims as originally filed. In particular, support for claim 1 may be found in originally filed claims 2-4; support for claim 11 may be found in originally filed claims 10 and 11 and at page 5, lines 29-34 of the specification; support for new claim 41 may be found at page 29, lines 22-24 of the specification; and support for new claim 42 may be found at page 5, lines 21-28 and at page 6, lines 26-34 of the specification.

Amendment and cancellation of the claims herein should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, or in any previous Office Action, and were done solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims as those originally filed in the instant application or in this or one or more or subsequent applications.

Priority

Applicants acknowledge that the present invention is entitled to claim priority to the applications cited by the Examiner on page 2 of the Office Action.

Specification

The Examiner objects to the typographical error on page 15, line 34 of the specification. In response, Applicants have amended the specification herein to remove this error.

Sequence Listing

The Examiner notes that the application claims a modified Factor VIII polypeptide, but no sequence information has been submitted. Applicants submit that the structure of the human Factor VIII polypeptide was well known to those skilled in the art at the priority date of the instant application and thus the specific amino acid sequence is not specifically set forth, and hence a Sequence Listing is not required. The sequence is however, incorporated by reference at page 2, lines 3-19 and at page 10, lines 16-35 of the specification.

Rejection of Claims 1-4, 8, 10, 11, and 13 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-4, 8, 10, 11, and 13 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. At page 3 of the Office Action, the Examiner inquires, "[i]s procoagulant-active FVIII a pro-FVIII protein (similar to a prohormone) or is it FVIII protein that is activated by thrombin?"

Applicants submit that the invention is directed to modified FVIII proteins, which may be activated by thrombin. With respect to the protein of claim 1, the protein is capable of secretion at levels higher than typically obtained with wild type FVIII and retains procoagulant activity (see, *e.g.*, page 5, lines 27-28 of the specification). With respect to the protein of claim 11, the protein is also capable of secretion at levels higher than typically obtained with wild type FVIII, retains procoagulant activity, and is APC resistant (see, *e.g.*, page 5, lines 33-34 and page 6, lines 26-29).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-4, and 8 Under 35 U.S.C. §102(a)

The Examiner rejects claims 1-4 and 8 under 35 U.S.C. §102(a) as being anticipated by Marquette *et al.* (*The Journal of Biological Chemistry*, Vol. 270, No. 17, pp. 10297-10303 April 28 (1995)). According to the Examiner,

> Marquette *et al.* teaches a procoagulant human Factor VIII protein that is modified at phenylalanine located at position 309 ... replacing the A1 domain of factor VIII (amino acids 226-335; Claim 1). The mutations taught are both a substitution (see above reference location; Claim 2) and a deletion mutation... The substituted mutation changes the phenylalanine at 309 with a serine residue... The Factor VIII protein was administered in a clotting assay as a pharmaceutical composition.

Applicants respectfully traverse. According to Marquette *et al.*, [c]himeric molecules were constructed replacing ...***factor VIII residues 1-336 with factor V residues 1-313*** (designated VIIIA1V). (see pg. 10299) *(Emphasis added)*. Thus, Marquette *et al.* teach deletion and replacement of *at least 336 residues* of the human Factor VIII protein, not a specific substitution of Phe309 with Ser, as now claimed by the present invention. Accordingly, Applicants respectfully request that the foregoing rejection is reconsidered and withdrawn.

Rejection of Claims 10 and 13 Under 35 U.S.C. §103(a)

The Examiner rejects claims 10 and 13 under 35 U.S.C. §103(a) as being obvious over Pittman *et al.* (*Proc. Natl. Acad. Sci.*, Vol. 85, pp. 2429-2433 (1988)) in view of Kaufman *et al.* (U.S. Patent No. 5,451,521). Applicants traverse the rejection. Claim 10 has been cancelled herein, without prejudice. However, with respect to claim 11, which includes elements of claim 10, neither Pittman *et al.* nor Kaufman *et al.* teach or suggest the pending claimed procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a substitution of the Arg residue at position 336 with Ile and a substitution of the Arg residue at position 562 with Lys, wherein the modification further comprises a mutation at position 309, and wherein said protein is APC resistant. Furthermore, Pittman *et al.* and Kaufman *et al.* do not teach or suggest a pharmaceutical composition comprising an effective amount of the claimed protein, as described above, in admixture with a parenterally acceptable vehicle or excipient. The Examiner is well-aware that in order to establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner

proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) ***must teach or suggest all the claim limitations.*** See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

While the Pittman *et al.* describes an Arginine to Isoleucine mutation at position 336 for the Factor VIII protein, it contains no teaching or suggestion to modify position 562 from Arginine to Lysine or a mutation at position 309, as required by claim 11. In addition, Pittman *et al.* does not teach or suggest that the claimed Factor VIII protein is APC resistant, and hence does not render the pending claims obvious.

Kaufman *et al.* also does not teach or suggest the pending claims nor provide the elements missing from Pittman *et al.* to teach or suggest the pending claims. Applicants agree that Kaufman *et al.* discloses a general teaching to modify any of positions 226, 336, 562, 740, 776, 1313, 1648, or 1721 of Factor VIII, however it does not teach or suggest specific modifications of the FVIII polypeptide, as claimed. In particular, Kaufman *et al.* does not teach a modification of the FVIII polypeptide comprising a substitution of the Arg residue at position 336 with Ile; a substitution of the Arg residue at position 562 with Lys; and a mutation at position 309. Furthermore, Kaufman *et al.* does not teach or suggest that such a polypeptide is APC resistant, let alone which modifications confer said resistance. Given that neither Pittman *et al.* nor Kaufman *et al.*, teach or suggest, either alone or in combination, the elements of the claimed procoagulant-active FVIII protein, it stands to reason that a pharmaceutical composition comprising such a procoagulant-active FVIII protein, as set forth in claim 11, has not been suggested or taught by the cited references. Applicants therefore request withdrawal of this § 103 rejection.

Rejection of Claim 11 Under 35 U.S.C. §103(a)

The Examiner has rejected claim 11 under 35 U.S.C. §103(a) as being obvious over Marquette *et al.* in view of Kaufman *et al.* According to the Examiner, "Marquette *et al.* teaches a procoagulant human Factor VIII protein that is modified at phenylalanine located at position 309 ... replacing the A1 domain of factor VIII (amino acids 226-335) that has improved secretion." The Examiner further indicates that Kaufman *et al.* teaches human Factor VIII protein that has modifications at Arginine 336 and 562. The Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time of the invention to make an inactivation resistant human Factor VIII protein with improved secretion."

Applicants traverse the rejection. Marquette *et al.* disclose deletion and replacement of *at least 336 residues* of the human Factor VIII protein, not a specific substitution at position 309, as now claimed by the present invention. Furthermore, while Kaufman *et al.* disclose the importance of several residues, the reference fails to provide any teaching or suggestion of the particular substitutions, *i.e.*, a modification comprising a substitution of the Arg residue at position 336 with Ile; a substitution of the Arg residue at position 562 with Lys; and a mutation at position 309, as claimed. Kaufman *et al.* does not teach or suggest that such a polypeptide is APC resistant, let alone which modifications confer said resistance. Furthermore, with respect to new claim 42, which is dependent on claim 11, neither reference teaches or suggests that such a modified FVIII protein is capable of increased secretion. Based on the teachings of Kaufman *et al.* and Marquette *et al.*, alone or in combination, it would not be obvious for the skilled artisan to arrive at the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. UMV-1184CPCN from which the undersigned is authorized to draw.

Dated: February 23, 2004

Respectfully submitted,

By _____

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